**A Direct, One Pot Synthesis of Imidazoles from Imines and Acid Chlorides:
A Palladium Catalyzed Multicomponent Coupling Approach**

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General Procedures

All reactions were carried out under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or using standard Schlenk techniques, unless otherwise indicated. Palladium catalysts (2) were prepared according to a previously reported procedure, by pretreating $\text{Pd}_2\text{dba}_3\text{CHCl}_3$ with imine and acid chloride.¹ Carbon monoxide (99.99%) was purchased from Matheson and used as received. N-alkyl and -aryl imines, and N-tosylimines, were prepared according to the literature procedures.^{2,3} All other reagents were purchased from Aldrich[®] and used as received. Acetonitrile was freshly purified by distillation over CaH_2 under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Deuterated solvents were dried over drying agents, transferred under vacuum and stored over 3 and 4 Å molecular sieves. ^1H and ^{13}C NMR were acquired on a Mercury 400 MHz spectrometer. Mass spectra were obtained from the McGill University Mass Spectral Facility.

General Procedure for the Catalytic Synthesis of Imidazoles 3

Imine (0.68mmol) and acid chloride (0.98mmol) in 5 mL of acetonitrile were added to a 50 mL reaction bomb, followed by the palladium catalyst (5 mol%) in 5 mL of acetonitrile, $\text{P}(o\text{Tol})_3$ (31.3mg, 0.102mmol) in 5 mL of THF, EtNiPr_2 (264mg, 2.04mmol) in 5 mL THF, N-tosyl imine (0.81mmol) and LiCl (87mg, 2.04 mmol). (The reaction with tBu(H)C=NBn was performed with 1 equiv. LiOTf). The entire solution was frozen in liquid nitrogen and evacuated, and carbon monoxide (60 psi) added. The mixture was heated at 45°C for 16h-18h. All imidazoles were purified by silica gel chromatography using hexane:ethylacetate:triethylamine as eluent.

Synthesis of 4-[5-(4-Fluoro-phenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-phenol SB202190 (3i)

4-FC₆H₄(H)C=N(CH₂CHCH₂) (111.5mg, 0.68 mmol) and anisoyl chloride (348mg, 2.04 mmol) in 5 mL acetonitrile were added to a 50 mL reaction bomb, followed by [Pd(Cl)[η²-CH(p-tolyl)NEt(COPh)]₂ (27mg, 0.034mmol) in acetonitrile (5mL), P(*o*-tol)₃ (31.3mg, 0.102mmol) in 5 mL of THF, EtN*i*Pr₂ (132mg, 1.02mmol) in 5mL of THF and LiCl (29mg, 0.68mmol). 4-pyridyl(H)C=NTs (158.1mg, 0.68mmol) in 3 mL of THF was slowly added to the reaction solution over a 10 min period. Carbon monoxide (60 psi) was introduced into the reaction bomb as described previously, and the solution was heated at 55°C for 28 h. The mixture was filtered through silica gel, redissolved in CH₂Cl₂ and transferred into a Schlenk tube under nitrogen, along with tetrakis(triphenylphosphine)palladium⁴ (5mol%) in 5 mL of CH₂Cl₂ and acetic acid (4eq.). Phenylsilane (2eq.) was added dropwise and the solution was stirred at room temperature and monitored by TLC until deallylation was completed (20h). The solvent was evaporated and the brownish residue dissolved in HBr 48% (20mL), NaI (2eq.) was added and the mixture was heated at 120 °C for 24h.⁵ The mixture was then quenched with Na₂CO₃ and pH was adjusted to 7-8. The crude product was extracted with CH₂Cl₂ (5 × 50 mL), dried over MgSO₄, and filtered. The product was purified by silica gel column chromatography using hexane:ethylacetate:triethylamine:methanol.

Spectroscopic Data on 3

1-Ethyl-2,4-diphenyl-5-p-tolyl-1H-imidazole (3a) Yield: 76% ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, 2H), 7.57(d, 2H), 7.50-7.43 (m, 3H), 7.33-7.28 (m, 4H), 7.22-7.18 (t, 2H), 7.14-7.10 (t, 1H), 3.96 (q, 2H), 2.46 (s, 3H), 1.05 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 147.3, 138.7, 137.7, 134.8, 131.6, 131.0, 129.9, 129.6, 129.3, 128.9, 128.7, 128.6, 128.1, 126.9, 126.3, 39.9, 21.8, 16.7. HRMS. Calculated for $\text{C}_{24}\text{H}_{22}\text{N}_2$: 338.17830; found: 338.17795.

4-Furan-2-yl-1-(4-methoxy-phenyl)-2,5-di-p-tolyl-1H-imidazole (3b) Yield: 71% ^1H NMR (400 MHz, CDCl_3): δ 7.36 (m, 1H), 7.32-7.30 (d, 2H), 7.06 (s, 4H), 7.04-7.02 (d, 2H), 6.9-6.92 (d, 2H), 6.76-6.74(d, 2H), 6.33-6.26 (d, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 159.1, 149.6, 147.5, 141.3, 138.3, 137.9, 131.0, 130.9, 130.8, 129.9, 129.5, 129.0, 128.9, 127.6, 127.0, 114.4, 111.0, 105.8, 55.7, 21.8, 21.7. HRMS. Calculated for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_2$: 420.18378; found: 420.18436.

1-Benzyl-5-tert-butyl-4-phenyl-2-p-tolyl-1H-imidazole (3c) Yield: 67% ^1H NMR (400 MHz, CDCl_3): δ 7.45 (m, 3H), 7.36-7.33 (m, 4H), 7.25-7.29 (t, 3H), 7.09(d, 2H), 6.83 (d, 2H), 5.59 (s, 2H), 2.35 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 146.5, 145.0, 143.0, 138.9, 136.6, 135.6, 134.0, 131.5, 130.5, 130.1, 130.0, 129.6, 128.7, 128.5, 125.3, 51.0, 33.5, 31.8, 21.7. HRMS. Calculated for $\text{C}_{27}\text{H}_{28}\text{N}_2$: 380.22525; found: 380.22468

1-Hexyl-2-phenyl-4-thiophen-2-yl-5-p-tolyl-1H-imidazole (3d) Yield: 70% ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.65 (m, 2H), 7.49-7.42 (m, 3H), 7.36-7.30 (m, 4H), 7.05-7.04 (m, 1H), 6.94-6.93 (d, 1H), 6.86-6.84 (m, 1H), 3.85 (t, 2H), 2.47 (s, 3H), 1.36 (m, 2H), 1.07 (m, 2H), 0.96 (m, 4H), 0.75 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 147.5, 139.1, 138.5, 133.6, 131.4, 131.2, 129.9, 129.4, 129.0, 128.8, 128.7, 127.8, 127.1, 123.1, 122.5, 45.1, 31.1, 30.7, 26.2, 22.6, 22.0, 14.3. HRMS. Calculated for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{S}$: 400.19732; found: 400.19706

1-Ethyl-2-isopropyl-4-phenyl-5-p-tolyl-1H-imidazole (3e) Yield: 60% ^1H NMR (400 MHz, CDCl_3): δ 7.78-7.74 (d, 1H), 7.64-7.61 (m, 2H), 7.48-7.46 (d, 2H), 7.42-7.41 (m, 2H), 7.19-7.1 (m, 2H), 3.82-3.77 (q, 2H), 3.09-3.05 (m, 1H), 2.42 (s, 3H), 1.47-1.45 (d, 6H), 1.14-1.11 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.0, 143.5, 135.0, 131.1, 130.7, 130.1, 129.2, 128.6, 128.4, 127.4, 125.6, 39.0, 26.7, 22.0, 21.6, 16.7. HRMS. Calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2$: 304.19395; found: 304.19334

3-[1-Ethyl-2-furan-2-yl-5-(4-methylsulfanyl-phenyl)-1H-imidazol-4-yl]-pyridine (3f) Yield:

70% ^1H NMR (400 MHz, CDCl_3): δ 8.61 (s, 1H), 8.34 (d, 1H), 7.86-7.84 (d, 1H), 7.52 (s, 1H), 7.32-7.30 (d, 2H), 7.26-7.24 (d, 2H), 7.14-7.11 (dd, 1H), 6.94-6.93 (d, 1H), 6.54-6.53 (m, 1H), 4.09 (q, 2H), 2.52 (s, 3H), 1.22 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 148.0, 147.4, 145.6, 143.0, 140.6, 139.1, 135.5, 134.0, 131.3, 130.4, 130.2, 126.7, 126.3, 123.3, 111.8, 110.2, 40.3, 16.8, 15.6. HRMS. Calculated for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{OS}$: 361.12488; found: 361.12452

1-Ethyl-2-phenyl-4-styryl-5-p-tolyl-1H-imidazole (3g) Yield: 74% ^1H NMR (400 MHz,

CDCl_3): δ 7.77-7.68 (d, 2H), 7.49-7.40 (m, 6H), 7.33 (s, 4H), 7.28-7.24 (t, 2H), 7.15 (t, 1H), 6.92-6.88 (d, 1H), 4.01 (q, 4H), 2.47 (s, 3H), 0.96 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 148.4, 138.5, 138.3, 137.2, 132.0, 131.5, 130.6, 129.7, 129.4, 129.1, 128.8, 128.6, 127.2, 127.0, 126.8, 126.4, 119.7, 40.1, 21.8, 16.5. HRMS. Calculated for $\text{C}_{26}\text{H}_{24}\text{N}_2$: 364.19395; found: 364.19274

4-Cyclohexyl-1-ethyl-2,5-di-p-tolyl-1H-imidazole (3h) Yield: 68% ^1H NMR (400 MHz,

CDCl_3): δ 7.5 (d, 2H), 7.27-7.22 (m, 6H), 3.8 (q, 2H), 2.44 (s, 3H), 2.40 (s, 3H), 1.74 (s, broad, 7H), 1.62 (s, broad, 1H), 1.25 (s, broad, 3H), 0.97 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ

146.4, 144.6, 138.4, 138.0, 130.8, 129.3, 129.29, 129.27, 129.23, 128.7, 127.9, 39.8, 36.9, 33.5, 27.1, 26.3, 21.7, 16.6. HRMS. Calculated for $C_{25}H_{30}N_2$: 358.24090; found: 358.24040

4-Butyl-1-ethyl-2-(4-methoxy-phenyl)-5-p-tolyl-1H-imidazole (3i) Yield: 69% 1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (d, 2H), 7.25-7.23 (m, 4H), 6.96-6.94 (d, 2H), 3.92 (q, 2H), 3.82 (s, 3H), 2.51 (t, 2H), 2.40 (s, 3H), 1.61 (m, 2H), 1.30 (m, 2H), 0.95 (t, 3H), 0.85 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 146.5, 139.6, 137.8, 130.52, 130.51, 129.4, 128.8, 128.3, 124.3, 114.0, 55.6, 39.9, 33.0, 27.5, 23.1, 21.7, 16.5, 14.3. HRMS. Calculated for $C_{23}H_{28}N_2O$: 348.22016; found: 348.22045

4-[5-(4-Fluoro-phenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-phenol (3j) Yield: 65% 1H NMR (400 MHz, CD_3OD): δ 8.41 (s, broad, 2H), 7.83 (d, 2H), 7.51 (q, 4H), 7.2 (t, 2H), 6.88 (d, 2H), 3.34 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 164.9, 161.7, 158.8, 148.81, 148.80, 138.8, 130.9, 130.8, 127.5, 121.9, 121.03, 115.7, 115.5, 115.49, 109.9. HRMS. Calculated for $C_{20}H_{14}FN_3O$: 331.11209; found: 331.11145

4-Benzo[1,3]dioxol-5-yl-1-ethyl-2-phenyl-5-p-tolyl-1H-imidazole (3k) Yield: 72% ^1H NMR (400 MHz, CDCl_3): δ 7.69 (d, 2H), 7.49-7.42 (m, 3H), 7.29 (s, 4H), 7.07 (d, 1H), 7.03 (s, 1H), 6.67 (d, 1H), 5.86 (s, 2H), 3.92 (q, 2H), 2.44 (s, 3H), 1.03 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 147.4, 147.02, 146.06, 138.7, 137.5, 131.5, 131.08, 130.04, 129.3, 129.2, 128.9, 128.8, 128.7, 128.5, 120.6, 108.2, 107.7, 100.8, 39.9, 21.8, 16.7. HRMS. Calculated for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2$: 382.16813; found: 382.16756

5-(4-Fluoro-phenyl)-1-(4-methoxy-benzyl)-4-phenyl-2-thiophen-2-yl-1H-imidazole (3l)

Yield: 71% ^1H NMR (400 MHz, CDCl_3): δ 7.54-7.52 (d, 2H), 7.36-7.35 (d, 1H), 7.26-7.20 (m, 2H), 7.19-7.15 (m, 4H), 7.04-6.99 (m, 3H), 6.86-6.80 (m, 4H), 5.11 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 159.1, 142.4, 138.7, 134.3, 133.1, 133.0, 132.9, 129.2, 128.4, 127.7, 127.2, 127.1, 127.0, 126.8, 126.3, 116.4, 116.1, 114.5, 55.5, 47.9. HRMS. Calculated for $\text{C}_{27}\text{H}_{21}\text{FN}_2\text{OS}$: 440.13586; found: 440.13552

3-(2-Phenyl-1-thiophen-2-ylmethyl-5-p-tolyl-1H-imidazol-4-yl)-pyridine (3m) Yield: 70%

^1H NMR (400 MHz, CDCl_3): δ 8.66 (s, 1H), 8.38 (s, 1H), 8.16 (d, 1H), 7.69-7.66 (m, 2H), 7.48-7.46 (m, 2H), 7.33-7.30 (m, 2H), 7.26-7.24 (d, 2H), 7.19-7.17 (d, 2H), 7.13-7.11 (d, 1H), 6.79-6.77 (m, 1H), 6.40-6.39 (d, 1H), 5.22 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 148.7, 139.9, 139.5, 136.2, 134.0, 131.8, 130.8, 130.69, 130.66, 130.4, 129.7, 129.6, 129.4, 129.3, 129.0, 126.9, 126.6, 125.9, 125.6, 124.2, 44.0, 21.7. HRMS. Calculated for $\text{C}_{26}\text{H}_{21}\text{N}_3\text{S}$: 407.14562; found: 407.14500

4-Benzo[1,3]dioxol-5-yl-1-benzyl-2-phenyl-5-p-tolyl-1H-imidazole (3n) Yield: 73%

^1H NMR (400 MHz, CDCl_3): δ 7.65-7.63 (m, 2H), 7.38-7.37 (m, 3H), 7.21-7.19 (m, 3H), 7.16-7.11 (m, 3H), 7.09-7.07 (m, 3H), 6.82-6.80 (m, 2H), 6.70-6.68 (d, 1H), 5.87 (s, 2H), 5.08 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 147.65, 147.56, 146.4, 138.8, 137.7, 131.3, 131.1, 129.8, 129.6, 129.5, 129.28, 129.23, 129.1, 128.8, 128.7, 127.6, 126.2, 120.8, 108.3, 107.7, 100.9, 48.5, 21.6. HRMS. Calculated for $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_2$: 444.18378; found: 444.18324

Reaction of N-acyliminium salt 6 with NaSO₂Tol

p-tolylC₆H₄(H)C=NEt (40mg, 0.272mmol) and benzoyl chloride (53.5mg, 0.38mmol) were dissolved in 10 mL of acetonitrile and stirred at room temperature for 10 min. The formation of iminium salt **6** was confirmed by ¹H NMR spectroscopy. To this solution was added *p*-toluene sulfinic acid sodium salt (48.4mg, 0.272mmol), and the mixture was stirred at room temperature for 2 h. ¹H NMR shows the quantitative formation of 4-Methyl-benzenesulfinic acid (benzoyl-ethyl-amino)-*p*-tolyl-methyl ester **4**. ¹H NMR (400 MHz, CDCl₃): δ 7.63 (m, broad, 4H), 7.37-7.24 (m, 5H), 7.20-7.18 (d, 2H), 7.11-7.09 (d, 2H), 3.93-3.88 (m, 2H), 2.37 (s, broad, 3H), 2.35 (s, 3H), 0.672 (s, broad, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 172.1, 145.1, 139.9, 135.9, 135.5, 130.3, 129.88, 129.86, 129.84, 129.2, 128.4, 127.6, 126.7, 78.6, 40.01, 21.94, 21.56, 14.9. Calculated for C₂₄H₂₅NO₃SNa⁺: 430.1, ESI-MS: 429.7 *m/z*

Thermal Decomposition of 6

p-TolC₆H₄(H)C=NEt (40mg, 0.272mmol) and benzoyl chloride (53.5mg, 0.38mmol) were dissolved in 10 mL of acetonitrile and stirred at room temperature for 10 min in a 50 mL reaction bomb. To this solution was added EtNiPr₂ (105.47mg, 0.816mmol) and the reaction solution was heated at 65 °C for 12 h. The formation of N-ethyl-benzamide **5** was confirmed by ¹H NMR spectroscopy (63%).

Reaction of 4 with LiCl

A solution of 4-Methyl-benzenesulfinic acid (benzoyl-ethyl-amino)-*p*-tolyl-methyl ester **4** was prepared according to the procedure described above. To this solution was added LiCl 3 eq. (34.68mg, 0.816mmol) and the mixture was stirred at room temperature for ½ h. Analysis of the reaction solution by ¹H NMR spectroscopy demonstrates the regeneration of **6** in 79 % yield.

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Compound **3a**, ^1H NMR spectra

Compound **3b**, ^1H NMR spectra

Compound **3c**, ^1H NMR spectra

Compound **3d**, ^1H NMR spectra

Compound **3e**, ^1H NMR spectra

Compound **3f**, ^1H NMR spectra

Compound **3g**, ^1H NMR spectra

Compound **3h**, ^1H NMR spectra

Compound **3i**, ^1H NMR spectra

Compound **3j**, ^1H NMR spectra

Compound **3k**, ^1H NMR spectra

Compound **3l**, ^1H NMR spectra

Compound **3m**, ^1H NMR spectra

Compound **3n**, ^1H NMR spectra

Compound 4, ^1H NMR spectra